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RESEARCH ARTICLE

Glycated hemoglobin A1c, cerebral small vessel disease burden, and disease severity in Parkinson's disease

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Abstract

Objective: Our study aimed to investigate the glucose levels in PD and controls. We also examine whether glucose control is associated with PD severity regardless of diabetic status, and test whether the correlation is mediated by cerebral small vessel disease (CSVD) burden. **Methods**: A total of 100 patients with idiopathic PD and 100 age- and sex-matched controls who underwent brain magnetic resonance imaging (MRI) were enrolled in this study. We collected the clinical data and blood parameters, including fasting blood glucose (FBG), glycated hemoglobin A1c (HbA1c), and blood lipid. Patients with PD were divided into early (n = 61) and advanced (n = 39) subgroups, based on Hoehn and Yahr (H&Y) stages. Differences between the PD and controls, PD with and without diabetes, and between two PD subgroups were compared. CSVD markers were assessed, including lacunes, white matter hyperintensities, enlarged perivascular spaces, and cerebral microbleeds. Multivariable logistic regressions were used to test the association between HbA1c and H&Y stages. Interaction between HbA1c and CSVD burden in relation to H&Y stages was also analyzed. **Results**: PD group exhibited higher HbA1c ($p < 0.001$), lower high-density lipoprotein cholesterol ($p < 0.001$) and triglyceride ($p = 0.049$) than controls. Advanced PD patients showed higher HbA1c than early PD group ($p = 0.022$). Increasing HbA1c (OR = 1.54, 95% CI 1.03–2.32, $p = 0.036$) along with longer disease duration (OR = 1.14, 95% CI 1.01–1.27, $p = 0.028$) and higher UPDRS III score (OR = 1.07, 95% CI 1.02–1.11, $p = 0.002$) increased the risk of belonging to the higher H&Y stage. However, interaction between HbA1c and CSVD burden in relation to H&Y stages was not significant. **Interpretation**: HbA1c is independently associated with H&Y stages in PD, and this correlation may not be mediated by CSVD burden.

Introduction

The correlation between Parkinson's disease (PD) and diabetes mellitus (DM) has receiving more and more attention recently. Whether DM is a risk factor or protective factor for PD remains conflicting.[1–3] Previous studies have provided evidences supporting the role of Type 2 diabetes in PD progression.[1] However, the underlying mechanisms are still unknown.

Previous work has suggested shared pathogenic pathways between PD and cerebrovascular diseases, such as cerebral small vessel disease (CSVD).[4] On brain MRI, the CSVD markers mainly include lacunes, white matter hyperintensities (WMH), enlarged perivascular spaces (EPVS), and cerebral microbleeds (CMBs).[5] In addition, the total CSVD score has been considered as a more complete estimate of the full impact of CSVD on the brain, which might be better than separately measuring only one or two features.[6,7] CSVD burden has been shown to contribute to motor impairment, cognitive dysfunction, and affective disorders in PD.[8,9] Our previous study also indicated that higher H&Y stage was independently correlated with increased PVWMH score, and total CSVD score, after adjustment for multiple confounders.[10] These findings suggested that comorbid CSVD may be an aggravating factor for the progression of PD. Furthermore, diabetes mellitus

was related to increased DWMH, EPVS, and total CSVD burden in PD.[10] Elevated glycemia has shown to contribute to endothelial inflammation and vascular dysfunction, and has been considered as a risk factor of cardiovascular diseases.[11] Hence, we hypothesized that hyperglycemia might be correlated with disease severity in PD, which may be mediated by the CSVD burden on MRI.

In this study, our aim is to evaluate the glucose levels in PD and controls. We also investigate whether glucose control is associated with PD severity, and test whether the correlation is mediated by the CSVD burden. This study may help us to unravel the role of vascular risk factors in PD and shed new light on potential disease prevention and treatment of PD.

Methods

Subjects and clinical assessments

Patients with a diagnosis of clinically definite PD[12] were eligible from January 2017 to November 2022. All patients were diagnosed by neurologists specializing in movement disorders (Haibo Chen and Wen Su). A group of healthy age- and sex-matched individuals served as controls (NCs). We excluded patients who had parkinsonism syndrome induced by cerebrovascular disease, medications, trauma, encephalitis, poisoning, and other neurodegenerative diseases. Participants with severe internal medicine diseases (n = 2), and incapable of undergoing brain MRI examination (n = 6) were also excluded from the study. All 100 PD patients (96 were inpatients and 4 were outpatients) and 100 controls (all were outpatients) were assessed in the hospital. All participants were right-handed, and were evaluated by two well-trained raters in our study, with good consistence. Body mass index, history of stroke, and vascular risk factors were recorded, including hypertension, diabetes mellitus, hyperlipidemia, coronary heart disease, and smoking status. The disease duration, Mini-Mental State Examination (MMSE) score, Unified Parkinson's Disease Rating Scale (UPDRS) part III score, and Hoehn and Yahr (H&Y) stages of PD patients were collected. They were examined in the clinically defined "OFF" state. Moreover, according to H&Y stages, PD patients were divided into early group (H&Y 1–2) and advanced group (H&Y 2.5–4). Our study was approved by a local ethics committee (2021BJYYEC-258-02), and written informed consent was obtained from each participant after a detailed description of the study was provided.

Laboratory assessment

Blood samples were drawn in the morning after an overnight fast and measured the level of fasting blood glucose (FBG), glycated hemoglobin A1c (HbA1c), total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C).

MR image acquisition

All MRI examinations were performed using a 3.0 T MRI scanner (Achieva TX). Sequences consisted of T1-weighted [repetition time/echo time (TR/TE) = 2082 / 25 ms, field of view (FOV) = 24 cm × 24 cm, matrix = 512 × 512, and 5 mm slice thickness, and 1.5 mm slice gap], T2-weighted (T2WI, TR/TE = 2500 / 100 ms; FOV = 24 cm × 24 cm, matrix = 256 × 256, 5 mm slice thickness, and 1.5 mm slice gap), fluid-attenuated inversion recovery (FLAIR; TR/TE = 8000 / 140 ms; FOV = 24 cm × 24 cm, matrix = 256 × 228, and 0 mm slice thickness without slice gap), diffusion-weighted imaging (DWI; TR/TE = 5,000 / 76.4 ms; matrix = 128 × 128, and 5 mm slice thickness), and susceptibility weighted imaging (SWI; TR/TE = 16 / 22 ms; flip angle (FA) = 15°, FOV = 24 cm × 24 cm, matrix = 240 × 240, and 2.8 mm slice thickness without slice gap).

MRI analysis

CSVD markers were assessed by two trained investigators blinded to the participants' clinical information, including lacunes, periventricular and deep WMH (PVWMH and DWMH), EPVS, and CMBs. Lacunes were defined as round or ovoid cerebrospinal fluid-filled cavities in the basal ganglia or white matter, usually 3–15 mm.[13,14] PVWMH and DWMH lesions were assessed using the Fazekas scale from 0 to 314. PVWMHs were graded as 0 = absence, 1 = "caps" or pencil-thin lining, 2 = smooth "halo" and 3 = irregular PVWMH extending into the deep white matter. DWMHs were defined as 0 = absence, 1 = punctate foci, 2 = beginning confluence of foci, 3 = large confluent areas.[15] EPVS referred to punctate hyperintensities on T2WI in the basal ganglia, and were rated as follows: 0 = no EPVS, 1 = < 10 EPVS, 2 = 11–20 EPVS, 3 = 21–40 EPVS, and 4 = > 40 EPVS.[16] CMBs are well-defined, round hypointensities, ≤10 mm on SWI images.[13] In addition, we calculated the total CSVD score ranging from 0 to 4. One point was added for each of the following: ≥1 lacunes, ≥1 CMBs, high-grade WMH (Fazekas score = 3 in PVWMH or ≥2 in DWMH), and moderate-to-severe EPVS (>10 in the basal ganglia).[6]

Statistics

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) software (version

26.0). Categorical variables are presented as percentages, and continuous variables as means with standard deviations or medians with interquartile ranges based on their distributions. Two-sample *t*-test or Mann–Whitney *U*-test, and chi-squared test were conducted to explore differences of continuous variables and categorical variables, respectively, between PD and controls, PD with and without DM subgroups, as well as early and advanced PD subgroups. Fisher's precision probability test was used when the expected count was less than 5. Analysis of variance (ANOVA) followed by post hoc tests or Kruskal–Wallis test, and chi-squared tests were conducted to examine differences between continuous and categorical variables, respectively, between PVWMH, DWMH, EPVS, and total CSVD burden subgroups. Matched conditional logistic regression analysis was conducted to explore whether higher FBG or HbA1c was the risk factor for PD. In PD group, correlation between clinical, biological results, and CSVD imaging markers were assessed with Spearman's coefficient. Subsequently, multivariable logistic regression analysis was performed between H&Y stages, and blood parameters (FBG, HbA1c, and blood lipid), clinical parameters, as well as CSVD imaging markers.

The interaction between HbA1c and CSVD burden in relation to H&Y stages was explored by multivariable logistic regression. The H&Y stages (H&Y 1–2 vs. H&Y 2.5–4) were used as dependent variables. HbA1c value, CSVD burden, and their interaction, as well as other variables showing significant association with H&Y stages were used as independent variables. Each CSVD imaging markers and the total CSVD burden entered the multivariable regression model separately. Furthermore, path analysis was conducted to investigate how much CSVD imaging markers mediated the effect of HbA1c level on severity in PD. The standardized coefficient (β) of HbA1c without a mediation effect (direct effect) and with a mediation effect (indirect effect) and the standardized coefficient (β) of the CSVD markers on the H&Y stages were calculated. Statistically significant was set at $p < 0.05$.

Results

Comparison between PD and controls

One hundred PD patients and 100 controls were enrolled in this study. There were no significant differences in age, sex ratio, and the proportion of DM between PD and controls. Controls had a higher BMI, higher proportion of hyperlipidemia, coronary heart disease, and current smoking. PD patients had a higher proportion of stroke history than controls. PD group exhibited higher HbA1c, lower HDL-C and TG than controls. Using group (PD or controls) as the dependent variable, conditional logistic regression analysis showed that HbA1c was a risk factor for PD, after controlling for age, sex ratio, BMI, and vascular risk factors (OR = 2.21, 95% CI 1.30–3.75, $p = 0.003$). Moreover, PD patients revealed higher proportion of lacunes, PVWMH, DWMH, EPVS, and total CSVD burden, as well as lower CMB than controls (Table 1).

Comparison between PD with and without DM subgroups

PD patients with DM ($n = 22$) was older than those without DM ($n = 78$) (median: 69.5 vs. 67.5 years, $p = 0.010$). These two subgroups did not differ in sex ratio, BMI, disease duration, H&Y stages, UPDRS III score, MMSE score. PD with DM group showed a higher proportion of lacunes ($p = 0.012$), higher FBG ($p = 0.015$), and HbA1c value ($p < 0.001$) than PD without DM group. There were not significant differences in PVWMH, DWMH, EPVS, CMB, and total CSVD burden score between two PD subgroups (Table 1).

Comparison between early and advanced PD groups

Advanced PD ($n = 39$) showed longer disease duration and higher UPDRS III score than early PD ($n = 61$). Mann–Whitney *U* showed that compared with early PD group, advanced PD group had higher HbA1c ($p = 0.022$). Two PD subgroups did not differ in age, sex ratio, BMI, FBG, serum lipid, MMSE scores, DM proportion, and other vascular risk factors. There were not significant differences in CSVD burden between these two groups (Table 2, Fig. 1).

Associations between the higher or lower H&Y stage and multidimensional parameters in PD

Spearman correlation analysis revealed that the higher H&Y stage (H&Y 2.5–4) positively correlated with increasing HbA1c ($rs = 0.230$, $p = 0.021$) (Fig. 2), higher UPDRS III ($rs = 0.396$, $p < 0.001$), and longer disease duration ($rs = 0.276$, $p = 0.005$). H&Y stage was not associated with age, sex ratio, BMI, stroke history, vascular risk factors, FBG, blood lipid, MMSE score, and CSVD imaging markers.

In the multivariate binary logistic regression, HbA1c, disease duration, and UPDRS part III score were selected as independent variables, because these parameters could have an effect on the stage of PD. Multivariable logistic regression model 1 adjusted for age, gender, and MMSE score; Model 2 further adjusted for BMI, stroke history, vascular risk factors, FBG, blood lipid, and CSVD

Table 1. Clinical, biological characteristics, and CSVD markers of the subjects.

	PD (n = 100)	Controls (n = 100)	p value PD vs. controls	Non-DM–PD (n = 78)	DM–PD (n = 22)	p value non-DM–PD vs. DM–PD
Age (years)	68.0 (64.2–73.0)	68.0 (64.2–73.0)	0.955	67.5 (62.0–72.0)	69.5 (67.8–76.2)	0.010
Sex (M/F)	60/40	64/36	0.662	31/47	9/13	0.921
BMI (kg/m^2)	23.3 (21.7–25.6)	24.6 (22.4–26.5)	0.013	23.5 (21.8–25.8)	22.9 (21.2–24.8)	0.277
Vascular risk factors						
Current smoking (%)	3 (3.0)	3 (4.0)	<0.001	2 (2.6)	1 (4.5)	0.600
HTN (%)	40 (40.0)	48 (48.0)	0.319	29 (37.2)	11 (50.0)	0.328
DM (%)	22 (22.0)	15 (15.0)	0.274	NA	NA	NA
HL (%)	27 (27)	80 (80.0)	<0.001	21 (26.9)	6 (27.3)	0.974
CHD (%)	9 (9.0)	23 (23.0)	0.011	7 (9.0)	2 (9.1)	0.987
Stroke (%)	9 (9.0)	1 (1.0)	0.018	9 (11.7)	0 (0.0)	0.207
Dur (years)	4 (2–7)	NA	NA	4 (2–7)	4 (2–8)	0.812
UPDRS III	27 (18–35)	NA	NA	26 (16–34)	31 (21–37)	0.355
H&Y	2 (1.5–3)	NA	NA	2 (1.5–3)	2 (2–3)	0.143
MMSE	28 (27–29)	NA	NA	28 (26–29)	29 (28–29)	0.215
Biological assessment						
FBG (mmol/L)	5.30 (4.92–5.98)	5.46 (5.07–5.83)	0.346	5.20 (4.90–5.60)	6.45 (5.60–7.90)	0.015
HbA1c (%)	6.0 (5.6–6.6)	5.67 (5.43–5.94)	<0.001	5.8 (5.5–6.3)	7.0 (6.6–8.0)	<0.001
TC (mmol/L)	4.12 (3.62–4.82)	3.91 (3.55–4.59)	0.237	4.19 (3.66–4.83)	4.09 (3.46–4.56)	0.436
TG (mmol/L)	0.95 (0.72–1.44)	1.13 (0.91–1.51)	0.049	0.95 (0.66–1.46)	0.96 (0.77–1.27)	0.691
LDL-C (mmol/L)	2.48 (1.91–2.94)	2.34 (2.01–3.18)	0.470	2.46 (1.91–3.16)	2.52 (1.71–2.74)	0.450
HDL-C (mmol/L)	1.22 (1.04–1.42)	1.40 (1.22–1.66)	<0.001	1.24 (1.05–1.43)	1.18 (0.88–1.43)	0.669
MRI features						
The presence of lacunes (N, %)	24 (24.0)	6 (6.0)	0.001	14 (17.9)	10 (45.5)	0.012
PVWMH	1 (1–2)	1 (0–1)	<0.001	1.42 (0–3)	1.36 (0–3)	0.699
DWMH	1 (0–1)	1 (0–1)	0.010	0.87 (0–2)	1.05 (0–2)	0.306
EPVS	1 (1–1.75)	1 (1–1)	<0.001	1.26 (0–3)	1.36 (0–3)	0.590
The presence of CMBs (N, %)	10 (10.0)	23 (23.0)	0.021	9 (11.5)	1 (4.5)	0.573
CSVD burden	0 (0–1)	0 (0–1)	0.019	0.77 (0–4)	0.95 (0–4)	0.440

Data are expressed as n (%) or median (IQR) as appropriate.

BMI, body mass index; CHD, coronary heart disease; CMBs, cerebral microbleeds; CSVD, cerebral small vessel disease; DM, diabetes mellitus; Dur, disease duration; DWMH, deep white matter hyperintensities; EPVS, enlarged perivascular spaces; FBG, fasting blood glucose; H&Y, Hoehn and Yahr stages; HbA1c, glycated hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; HL, hyperlipidemia; HTN, hypertension; LDL-C, low-density lipoprotein cholesterol; MMSE, Mini-Mental State Examination; NA, not applicable; PD, Parkinson's disease; PVWMH, periventricular white matter hyperintensities; TC, total cholesterol; TG, triglyceride; UPDRS III, Unified Parkinson's Disease Rating Scale part III.

imaging markers in addition to Model 1.Using early or advanced PD group as the dependent variable (outcome), multivariate binary logistic regression revealed that increasing HbA1c (OR = 1.54, 95% CI 1.03–2.32, p = 0.036) along with longer disease duration (OR = 1.14, 95% CI 1.01–1.27, p = 0.028) and higher UPDRS III score (OR = 1.07, 95% CI 1.02–1.11, p = 0.002) increased the risk of belonging to the higher H&Y stage (advanced PD group) (Table 3).

Group comparisons of clinical parameters stratified by different CSVD markers in PD

PD patients with lacunes showed older age (71.75 ± 5.75 vs. 66.74 ± 7.53, p = 0.003), and lower MMSE score (25.21 ± 5.35 vs. 27.92 ± 1.98, p = 0.022) than those without lacunes. In the partial correlation analysis, after controlling the effect of age, PD with and without lacunes still correlated with MMSE score (r = −0.329, p = 0.001). There were no significant differences in BMI, FBG, HbA1c, serum lipid, UPDRS III, H&Y stages, disease duration, and MMSE scores between PWMH, DWMH, EPVS, CMB, and total CSVD burden subgroups.

Multivariate binary logistic regression analysis was performed between the presence of lacunes and clinical as well as blood parameters. The status of DM (OR = 18.30, 95% CI 2.44–137.44, p = 0.005, stroke history (OR = 47.43, 95% CI 2.52–892.02, p = 0.010), and MMSE score (OR = 0.62, 95% CI 0.43–0.89, p = 0.010) were associated with the presence of lacunes in patients with PD, after adjusted for age, gender, BMI, vascular risk factors except for DM, FBG, blood lipid, disease duration, UPDRS III, and H&Y stages. HbA1c was not found to be related with any CSVD imaging markers.

Table 2. Clinical, biological characteristics, and CSVD markers of early and advanced Parkinson's disease.

	Early PD (n = 61)	Advanced PD (n = 39)	p value
Age (years)	68.0 (64.5–73.0)	68.0 (64.0–72.0)	0.993
Sex (M/F)	39/22	21/18	0.403
BMI (kg/m^2)	23.4 (21.9–25.6)	22.8 (21.0–25.7)	0.314
Vascular risk factors			
Current smoking (%)	3 (4.9)	0 (0.0)	0.259
HTN (%)	26 (42.6)	14 (35.9)	0.537
DM (%)	11 (18.0)	11 (28.2)	0.322
HL (%)	15 (24.6)	12 (30.8)	0.645
CHD (%)	7 (11.5)	2 (5.1)	0.476
Stroke (%)	7 (11.5)	2 (5.1)	0.476
Dur (years)	3 (1–7)	6 (3–8)	0.034
UPDRS-III	23 (16–30)	34 (24–41)	<0.001
H&Y	2 (1.5–2)	3 (2.5–3)	<0.001
MMSE	28 (27–30)	27 (26–29)	0.405
Biological assessment			
FBG (mmol/L)	5.40 (4.90–5.95)	5.30 (5.00–6.00)	0.918
HbA1c (%)	5.9 (5.5–6.4)	6.3 (5.7–7.3)	0.022
TC (mmol/L)	4.07 (3.52–4.61)	4.20 (3.88–4.91)	0.168
TG (mmol/L)	0.99 (0.66–1.45)	0.93 (0.72–1.43)	0.563
LDL-C (mmol/L)	2.39 (1.84–2.82)	2.58 (2.17–3.17)	0.159
HDL-C (mmol/L)	1.21 (1.02–1.37)	1.28 (1.05–1.47)	0.255
MRI features			
The presence of lacunes (N, %)	16 (26.2)	8 (20.5)	0.633
PVWMH	1 (1–2)	1 (1–2)	0.703
DWMH	1 (0–1)	1 (0–1)	0.977
EPVS	1 (1–2)	1 (1–1)	0.759
The presence of CMBs (N, %)	7 (11.5)	3 (7.7)	0.736
CSVD burden	1 (0–1)	0 (0–1)	0.173

Data are expressed as n (%) or median (IQR) as appropriate.
BMI, body mass index; CHD, coronary heart disease; CMBs, cerebral microbleeds; CSVD, cerebral small vessel disease; DM, diabetes mellitus; Dur, disease duration; DWMH, deep white matter hyperintensities; EPVS, enlarged perivascular spaces; FBG, fasting blood glucose; H&Y, Hoehn and Yahr stages; HbA1c, glycated hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; HL, hyperlipidemia; HTN, hypertension; LDL-C, low-density lipoprotein cholesterol; MMSE, Mini-Mental State Examination; NA, not applicable; PD, Parkinson's disease; PVWMH, periventricular white matter hyperintensities; TC, total cholesterol; TG, triglyceride; UPDRS III, Unified Parkinson's Disease Rating Scale part III.

Interaction between HbA1C and CSVD imaging markers

In multivariable logistic regression for interactive effect of HbA1c and lacunes on H&Y stages (H&Y 1–2 vs. H&Y 2.5–4), there was a significant main effect of HbA1c, but not lacunes and interactions between HbA1c and lacunes on H&Y stages. Similarly, there was a significant main effect of HbA1c, but not PVWMH, DWMH, EPVS, CMB, or total CSVD burden, as well as interactions between HbA1c and these CSVD imaging markers on higher H&Y stage in PD (Table 4). The correlation between HbA1c and H&Y stages may not be mediated by the burden of CSVD.

In path analysis, the correlation of HbA1c with CSVD imaging markers were not significant (Fig. 3). That is, the burden of CSVD was not found to mediate the HbA1c effect on the increasing H&Y stages.

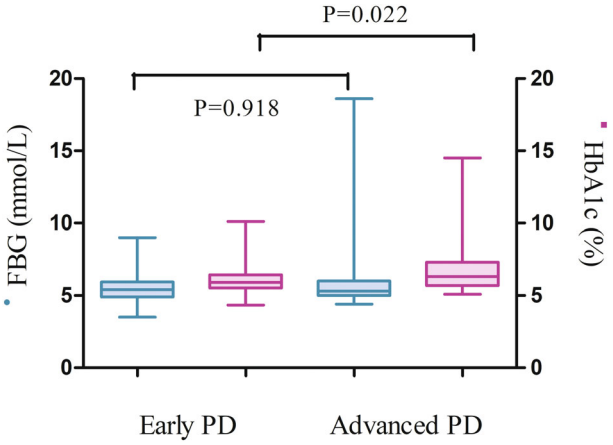

Figure 1. Differences in FBG and HbA1c between early and advanced PD groups. Mann–Whitney U-test was conducted to compare the differences in FBG and HbA1c level between early and advanced PD groups. FBG, fasting blood glucose; HbA1c, glycated hemoglobin A1c.

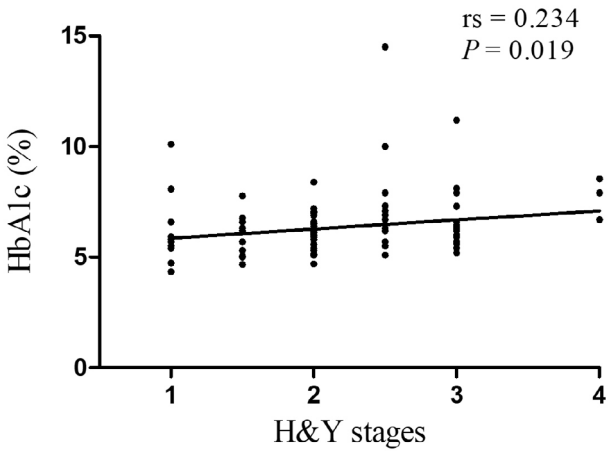

Figure 2. Spearman correlation between HbA1c and H&Y stages in PD. H&Y, Hoehn and Yahr stages; HbA1c, glycated hemoglobin A1c.

Discussion

This is the first study that investigated the relationship between glycated HbA1c, CSVD markers and disease

Table 3. Multivariate logistic regression for the lower or higher H&Y stage and clinical parameters in Parkinson's disease.

	Unadjusted		Multivariate logistic regression model 1		Multivariate logistic regression model 2	
Independent variable	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*
HbA1c	1.60 (1.08–2.38)	0.018	1.56 (1.03–2.37)	0.037	1.54 (1.02–2.30)	0.038
Disease duration	1.12 (1.00–1.24)	0.043	1.14 (1.01–1.27)	0.027	1.14 (1.02–1.28)	0.025
UPDRS III	1.07 (1.03–1.12)	<0.001	1.07 (1.02–1.11)	0.001	1.07 (1.03–1.11)	0.001

Multivariable logistic regression model 1 adjusted for age, gender, and MMSE score; Model 2 further adjusted for BMI, stroke history, vascular risk factors, FBG, blood lipid, and CSVD imaging markers in addition to Model 1.
Abbreviations: CI, confidence interval; CSVD, cerebral small vessel disease; FBG, fasting blood glucose; HbA1c, glycated hemoglobin A1c; H&Y stage, Hoehn and Yahr stage; UPDRS III, Unified Parkinson's Disease Rating Scale part III.

Table 4. Multivariable logistic regression for interactive effect of HbA1c and CSVD burden on H&Y stages.

	Model without interaction		Model with interaction	
	OR (95% CI)	*p* value	OR (95% CI)	*p* value
Model 1				
HbA1c	1.55 (1.02–2.34)	0.038	2.04 (1.10–3.80)	0.024
Lacunes	0.81 (0.27–2.40)	0.698	2.97 (0.20–4.29)	0.125
HbA1c × lacunes interaction	–		0.40 (0.13–1.24)	0.112
Model 2				
HbA1c	1.55 (1.04–2.33)	0.033	2.56 (0.95–6.90)	0.063
PVWMH	0.82 (0.47–1.44)	0.489	3.77 (0.28–51.25)	0.319
HbA1c × PVWMH interaction	–		0.79 (0.53–1.17)	0.242
Model 3				
HbA1c	1.53 (1.03–2.29)	0.037	2.49 (1.03–6.01)	0.043
DWMH	0.93 (0.48–1.84)	0.844	9.33 (0.27–32.71)	0.218
HbA1c × DWMH interaction	–		0.70 (0.41–1.20)	0.196
Model 4				
HbA1c	1.54 (1.03–2.32)	0.036	1.97 (0.76–5.10)	0.163
EPVS	0.62 (0.32–1.20)	0.154	1.63 (0.05–50.51)	0.782
HbA1c × EPVS interaction	–		0.86 (0.50–1.46)	0.576
Model 5				
HbA1c	1.55 (1.02–2.34)	0.039	1.67 (1.03–2.72)	0.038
CMB	0.40 (0.07–2.15)	0.285	18.63 (0–90.97)	0.595
HbA1c × CMB interaction	–		0.545 (0.10–3.11)	0.495
Model 6				
HbA1c	1.55 (1.03–2.33)	0.036	2.12 (1.08–4.14)	0.028
Total CSVD burden	0.85 (0.55–1.30)	0.449	3.74 (0.34–41.05)	0.281
HbA1c × total CSVD burden interaction	–		0.80 (0.55–1.15)	0.228

HbA1c, CSVD burden, and their interaction were fixed effect; disease duration and UPDRS III score were set as random effect.
CI, confidence interval; CMBs, cerebral microbleeds; CSVD, cerebral small vessel disease; DWMH, deep white matter hyperintensities; EPVS, enlarged perivascular spaces; H&Y, Hoehn and Yahr stages; HbA1c, glycated hemoglobin A1c; PVWMH, periventricular white matter hyperintensities.

severity in PD. The main finding indicated that HbA1c was independently associated with H&Y stages, but may not be mediated by the CSVD burden on MRI. This study suggests that hyperglycemia may be an aggravating factor for the progression of PD.

HbA1c can provide information about the average blood glucose levels during the last 3 months.[17] It may be more suitable than fasting blood glucose to reflect the glucose metabolism state. Previous study revealed no significant difference in diabetic status between PD and controls.[18] While another study indicated that PD patients had lower fasting plasma insulin (FPI) and increased fasting plasma amylin (FPA)/FPI ratio than controls. Moreover, there were no significant differences in fasting glycaemia and HbA1c between PD and controls.[19] In our study, higher HbA1c was found in PD

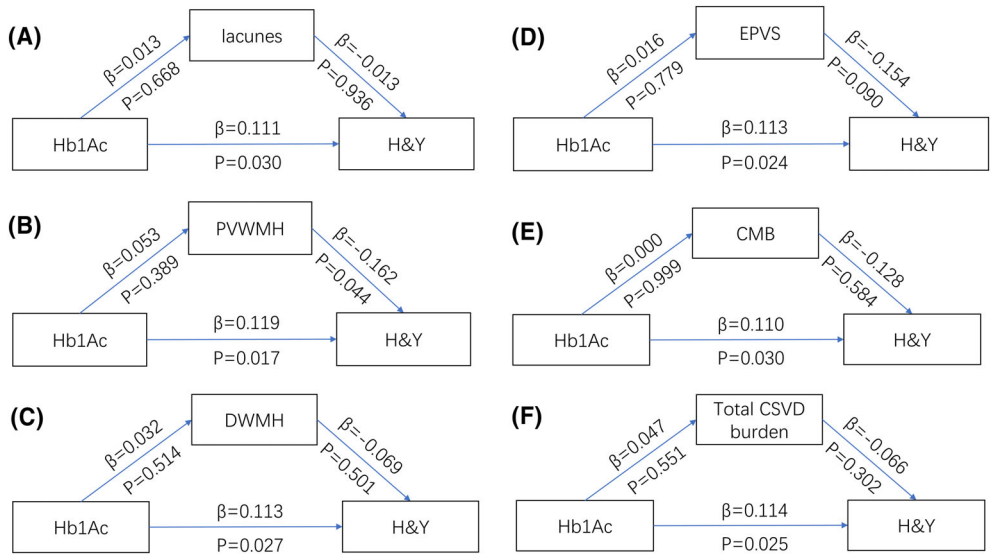

Figure 3. Path analysis. CMB, cerebral microbleeds; CSVD, cerebral small vessel disease; DWMH, deep white matter hyperintensities; EPVS, enlarged perivascular spaces; H&Y, Hoehn and Yahr stages; HbA1c, glycated hemoglobin A1c; PVWMH, periventricular white matter hyperintensities.

patients compared with controls, independently of diabetic status. Our findings supported the role of hyperglycemia in PD pathophysiology.

Glucose metabolic dysregulation has been found in moderate to advanced PD patients. Higher blood glucose levels markedly correlated with higher BMI, female gender, and longer disease duration.[20] In addition, associations have been observed between HbA1c and MDS-UPDRS III score, and between HbA1c and MoCA score in patients with both PD and Type 2 diabetes.[21] More importantly, high HbA1c was associated with a faster motor decline in two studies.[22,23] Also, there was an association between diabetes related to higher H&Y stages in PD.[24] Poorly controlled DM has been shown to be an independent risk factor of motor progression in PD.[25] Their findings shed new light on the importance of adequate control of diabetes, especially in monitoring serum HbA1c levels in PD.[25] As regards parkinsonism, PD patients exhibited higher proportion of impaired fasting glycemia and higher level of fasting glycemia than progressive supranuclear palsy (PSP) patients.[26] However, few studies have examined the association among HbA1c, CSVD burden, and disease severity in PD. Our study demonstrated that higher HbA1c levels correlated with PD severity, which may not be mediated by CSVD burden. Also, no significant associations between HbA1c and CSVD imaging markers were found. We could not confirm a markedly correlation between hyperglycemia, CSVD burden, and PD severity in our cohort, presumably due to other underlying confounding mechanisms. Several overlapping mechanisms of PD and hyperglycemia have been identified, including amyloid aggregation, microglial activation, chronic systemic inflammation, mitochondrial dysfunction, and impaired synaptic plasticity.[27] We speculate that there are other candidates for hyperglycemic effects on PD severity, except for increased comorbid microvascular pathology.

There were some limitations of this study. (1) This is a case–control study, and the sample size was relatively small. The relatively small number of the DM patients in PD and control group, and in patients with CSVD vascular burden may affect the power of the conclusions. Further larger sample size and prospective studies are needed to confirm our findings. (2) The subgroup analyses were similar to cross-sectional studies. There might be potential selection bias. (3) Hyperglycemia was used to assess glucose control. We could use other useful and straightforward indicators of glucose control and insulin resistance state, such as glucose tolerance test, and homeostasis model assessment index, in the future studies.

In conclusion, we found that HbA1c was independently associated with disease severity in PD, but not be mediated by CSVD burden. Hyperglycemia may be an aggravating factor for the progression of PD. Further studies are warranted to better understand this link and underlying pathways.

Author Contributions

Xinxin Ma: study design, neurological assessment, data analysis, and writing the manuscript. Shuhua Li: patients'

recruitment, and neurological assessment. Fengzhi Liu, Yu Du: neurological assessment. Haibo Chen: patients' recruitment and revising manuscript. Wen Su: study design and revising manuscript. All authors approved the final submitted version, and agree to be accountable for its content.

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Conflict of Interest

The authors have no conflict of interest to declare.

Data Availability Statement

The data supporting the findings of this study are available on request from the corresponding author.

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